REMARKS

This paper is responsive to the Office Action dated March 15, 2006, which is the first action on the merits of the application.

Claims 27-46 were previously pending in the application; claims 27-38 and 40 were under examination. Upon entry of this Amendment, certain claims are canceled, and claims 47-51 are added. The added claims fall within the group under examination. The amendments are supported by the specification and claims as previously presented, and do not add new matter to the disclosure. Reference to TERT promoter having 90% identity with the human TERT prototype (claim 33) is supported in the specification on page 7, lines 12-14. The amended claims cover a genus of TERT polynucleotides being homologous to the human TERT sequence (SEQ. ID NO:1). Previous election of human TERT as the species for initial examination in this application should not be taken to limit the scope of the claims as currently presented, beyond what is explicitly indicated. Reference to SEQ. ID NO:2 in claim 37 has been removed, thereby addressing the Objection made in the Office Action.

Accordingly, claims 27-33, 35-38, 40, 42-44 and 47-51 are now pending in the application, with claims 42-44 withdrawn from examination.

Further consideration and allowance of the application is respectfully requested.

Interview Summary

Applicant is grateful to Examiner Paul Dowell and Examiner Anne-Marie Falk for the cordial and constructive interview regarding this application held at the Office on May 16, 2006.

The undersigned proposed claim amendments that would overcome the rejections made under 35 USC §§ 112 ¶ 1 and 102. A Declaration under 37 CFR § 1.132 was discussed as a way of overcoming the rejections made under 35 USC § 103.

The claim amendments and remarks discussed at the interview are incorporated into this response. A 37 CFR § 1.132 Declaration by Dr. Calvin Harley will be filed in this application under separate cover, offering his expert opinion on the matters addressed here.

Rejections under 35 USC § 112 ¶ 1:

Claims 27, 38, and 40 stand rejected under the enablement and written description requirements of § 112 ¶ 1. The Office Action indicates that these claims read on *any* promoter polypeptide.

Applicant respectfully disagrees. The Office Action does not provide any example of a promoter (other than a TERT promoter) that has the same expression pattern as TERT — i.e., expression in most human cancer cells *of any tissue type*, and in some normal (non-cancerous) human stem cells, but *not* in mature human cells that do not express TERT. The specification illustrates the invention as previously claimed using SEQ. ID NO:1, SEQ. ID NO:2, and homologs thereof, and other suitable TERT promoter sequences that can be found without undue experimentation.

Nevertheless, to facilitate examination of this application, the claims have been amended to indicate that the promoter polynucleotide comprises the functional core sequence of SEQ. ID NO:1 (the promoter for human TERT), or a close homolog thereof. This is in accordance with what was found to satisfy the requirements of § 112 ¶ 1 for the hTERT promoter in priority application 09/244,438 (now U.S. Patent 6,777,203).

Claim 49 explicitly includes positions -117 to -36 of SEQ. ID NO:1. Thus, this claim need not recite further functional features beyond the fact that it is a *promoter sequence*, since the application discloses that constructs containing this part of the sequence drives transcription in cancer cells (page 2, lines 25-33, and Example 2).

Thus, the claims as currently presented comply with all the requirements of § 112 ¶ 1.

Rejection under 35 USC § 112 ¶ 2:

Claim 35 stands rejected under § 112 ¶ 2 for reasons of claim wording.

The claim has now been amended in accordance with the Examiner's recommendation, for which applicant is grateful. Withdrawal of this rejection is respectfully requested.

Rejections under 35 USC § 102:

Claims 27, 29, 31, 32, 35, and 40 stand rejected under § 102(e) as being anticipated by U.S. Patent 5,728,379 (Martuza et al.). Claims 27-32, 35, and 40 stand rejected under § 102(e) as being anticipated by U.S. Patent 5,998,205 (Hallenbeck et al.). The Office Action states that the HuH7 and HepG2 cell lines used in each of these disclosures inherently express TERT, and so the oncolytic

viruses disclosed in these references driven by any selective promoter would have all the features of the claimed invention.

Applicant respectfully disagrees. Whether or not the cell lines used in the cited references express TERT, this is not sufficient to establish that the constructs disclosed in the references have all the features previously claimed, as required to make a rejection under § 102. As stated above, the Office Action does not point to any promoter in the cited patents that has the same expression pattern as TERT (i.e., in most human cancer cells of any tissue type, and in some stem cells, but not in most mature cells). The working example in the Hallenbeck patent uses the α-fetoprotein promoter, which is expressed in hepatoma cells, but not in most other cancers nor in stem cells. The preferred promoters in the Martuza patent are from the growth hormone gene, expressed selectively in pituitary cells, and the pro-opiomelanocortin gene, expressed selectively in adrenocortical cells. None of these promoters meets the criteria required in the claims as previously presented.

In any event, these claims have now been amended to indicate explicitly that the promoter polynucleotide comprises the functional core sequence of SEQ. ID NO:1 (the promoter for human TERT), or a close homolog thereof. A TERT promoter is not used in either of the cited references.

Withdrawal of the rejections under 35 USC § 102 is respectfully requested.

Rejections under 35 USC § 103:

Claims 27-37 and 40 stand rejected under 35 USC § 103(a) as being obvious over U.S. Patent 5,998,205 (Hallenbeck et al.) and U.S. Patent 5,728,379 (Martuza et al.) as evidenced by articles by Kim et al. (Science 266:2011-2015, 1994) and Kanazawa et al (Biochem. Biophys. Res. Commun. 225:570-576, 1996) in view of an article by Takakura et al. (Cancer Res. 59:551-557, 1999). Alternatively, claims 27-37 and 40 stand rejected under § 103(a) as being obvious over the Hallenbeck and Martuza patents, in view of U.S. Patent 6,610,839 (Morin et al.).

The Hallenbeck patent generally discloses adenoviruses that conditionally replicate in cancer cells (referred to herein as an "oncolytic virus"). The Martuza patent generally discloses herpes viruses that conditionally replicate in cancer cells. The main premise of both rejections is that since it was known that TERT is expressed in cancer cells (as evidenced by Kim et al. and Kanazawa et al.), it would be obvious to substitute the human TERT promoter as taught by Takakura et al. or the Morin patent into oncolytic viruses according to the Hallenbeck or Martuza patents.

Applicant respectfully submits that this substitution is only obvious in hindsight from the invention disclosed and claimed in the present application[1]. At the time of filing, the claimed invention would not have been obvious to someone reading the cited references for the following reasons:

1. There was a large number of self antigens known at the time of filing to be preferentially expressed in tumor cells

Selective expression of certain human proteins in cancer cells has been extensively studied for over a century, and there are hundreds of markers proposed for use in cancer vaccines[2] or for selective expression of gene therapy vectors[3]. Any one of these promoters could be a candidate for driving the Hallenbeck or Martuza oncoviruses.

The mere fact that references *can* be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination[4]. It is well established in the law that a prior art reference disclosing a generic invention does not provide motivation to select a particular combination when there are a "vast number" of other alternatives[5].

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[1] For a prior art reference to be patent defeating, it must place the invention sought to be patented in the hands of the public without benefit of hindsight reconstruction of the patent application under consideration. "In order to render a claimed apparatus or method obvious, the prior art must enable one skilled in the art to make and use the apparatus or method." *Beckman Instruments, Inc. v. LKB Produkter AB*, 13 USPQ2d 1301 (Fed. Cir. 1989). Care must be taken to avoid hindsight reconstruction by using "the patent in suit as a guide through the maze of prior art references, combining the right references in the right way so as to achieve the result of the claims in suit." *Grain Processing Corp. v. American Maize-Products Corp.*, 5 USPQ2d 1788 (Fed. Cir. 1988).

[2] For example, Suresh MR. Classification of tumor markers. Anticancer Res. 1996 Jul-Aug;16(4B):2273-7. Durrant LG. Cancer vaccines. Anticancer Drugs. 1997 Sep;8(8):727-33.

[3] For example, Cooper MJ. Noninfectious gene transfer and expression systems for cancer gene therapy. Semin Oncol. 1996 Feb;23(1):172-87. Dachs GU, Dougherty GJ, Stratford IJ, Chaplin DJ. Targeting gene therapy to cancer: a review. Oncol Res. 1997;9(6-7):313-25. Patterson A, Harris AL. Molecular chemotherapy for breast cancer. Drugs Aging. 1999 Feb;14(2):75-90.

[4] *In re Mills*, 16 USPQ2d 1430 (Fed. Cir. 1990); *In re Fritch*, 23 USPQ2d 1780 (Fed. Cir. 1992). To establish a prima facie case of obviousness, . . . the Office is obligated to provide "evidence of the motivating force which would *impel* one skilled in the art to do what the patent applicant has done" (*Ex parte Levengood*, 28 USPQ2d 1300, 1302 (Bd. Pat. App. & Inter. 1993) (italics added).

[5] A prior art reference that disclosed a generic formula encompassing a claimed composition would not have provided the requisite motivation to select that composition because the reference (a) disclosed a "vast number" of possibilities, and (b) gave as "typical", "preferred", and "optimum" examples that "are different from and more complex than" the claimed composition. *In re Baird*, 29 USPQ2d 1550 (Fed. Cir. 1994).

2. The cited references teach against the claimed invention

The Hallenbeck and Martuza patent must be considered for all that they teach[6]. Each of these patents provides a number of alternative promoters that are suitable. Hallenbeck recommends and exemplifies four different promoters (Examples 1-4), while Martuza lists over sixty different promoters (Tables 1 & 2). Accordingly, the cited patents actually teach away from the invention claimed here — there are enough alternatives already suggested in the patents to occupy the attention and the budget of the skilled user for a very long time. The Office Action does not point to anything in the prior art that suggests TERT would be a better choice to the abundance of other promoters listed as preferred alternatives in the two cited patents.

3. The skilled reader would be concerned about potential dangers of using the TERT promoter

Even if someone reading the Hallenbeck and Martuza patents were to consider the possibility of the TERT promoter as yet another alternative, applicant respectfully submits that they would be dissuaded from selecting it because of potential risks. TERT is expressed in stem cells of various tissues[7] to allow these cells to replicate and replenish the tissue as needed. In theory, an oncolytic virus driven by the TERT promoter could potentially deplete such stem cell populations, leading to failure of tissues that regenerate on an ongoing basis, such as the hematopoietic system, the immune system, or the mucosal surface.

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[6] [A] prior art reference is relevant for all that it teaches to those of ordinary skill in the art. *In re Fritch*, 23 USPQ2d 1780 (Fed. Cir. 1992). A reference should be considered as a whole, and portions arguing against or teaching away from the claimed invention must be considered. *Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve, Inc.*, 230 USPQ 416 (Fed. Cir. 1986).

[7] Harley CB, Villeponteau B. Telomeres and telomerase in aging and cancer. Curr Opin Genet Dev. 1995 Apr;5(2):249-55.

4. Using the TERT promoter in an oncolytic virus has unexpected benefits

The specification of this application is the first disclosure to provide rationale and data for using the TERT promoter in an oncolytic virus. Subsequent experiments by applicant and by others not only confirm the viability of the claimed invention, but also show that it has unexpected benefits.

- Oncolytic adenovirus driven by the TERT promoter has a substantial clinical effect on tumors in animal models *after a single injection*[8].
- Despite the theoretical concern put forward in the last section, there were *no* observed side effects due to lysis of TERT expressing cells outside the tumor[9].
- The invention was effective in a disseminated lung tumor model (a model for *metastatic disease*)[10].
- The claimed invention *is more effective than ONYX-015*, an extensively studied vector developed for commercial use that replicates selectively in p53 mutated cells[11].

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[8] Lanson NA Jr, Friedlander PL, Schwarzenberger P, Kolls JK, Wang G. Replication of an adenoviral vector controlled by the human telomerase reverse transcriptase promoter causes tumor-selective tumor lysis. Cancer Res. 2003 Nov 15;63(22):7936-41.

[9] Irving J, Wang Z, Powell S, O'Sullivan C, Mok M, Murphy B, Cardoza L, Lebkowski JS, Majumdar AS. Conditionally replicative adenovirus driven by the human telomerase promoter provides broad-spectrum antitumor activity without liver toxicity. Cancer Gene Ther. 2004 Mar;11(3):174-85. Huang Q, Zhang X, Wang H, Yan B, Kirkpatrick J, Dewhirst MW, Li CY. A novel conditionally replicative adenovirus vector targeting telomerase-positive tumor cells. Clin Cancer Res. 2004 Feb 15;10(4):1439-45. Kuppuswamy et al., *infra*.

[10] Kuppuswamy M, Spencer JF, Doronin K, Tollefson AE, Wold WS, Toth K. Oncolytic adenovirus that overproduces ADP and replicates selectively in tumors due to hTERT promoter-regulated E4 gene expression. Gene Ther. 2005 Nov;12(22):1608-17.

[11] Wirth T, Zender L, Schulte B, Mundt B, Plentz R, Rudolph KL, Manns M, Kubicka S, Kuhnel F. A telomerase-dependent conditionally replicating adenovirus for selective treatment of cancer. Cancer Res. 2003 Jun 15;63(12):3181-8.

Before the filing of the priority application in 1999, there was no prediction by others that an oncolytic virus driven by the TERT promoter would have these features. Unexpected results provide evidence of non-obviousness[12], and there is no requirement that such results be disclosed in the application as filed[13].

To reflect the fact that the claimed oncolytic viruses of this invention are particularly effective at eliminating cancer cells *in vivo* without risking the stem cell population, the claims have now been amended to refer explicitly to replication in cancer cells.

For any and all of these reasons, applicant respectfully submits that the claimed invention is not obvious over any of the cited references considered alone or in any combination.

The foregoing amendments, arguments and accompanying documents are sufficient in and of themselves to overcome both the rejections made under 35 USC § 103.

Nevertheless, as suggested in the Office Action, the Morin patent does not qualify as a prior art reference by virtue of § 103(c)(1). Specifically, all of the inventors on this application and the cited patent were employees of Geron Corporation at the time the respectively claimed inventions were made, and were under obligation to assign the inventions to Geron Corporation as part of their employment relationship. In compliance with this obligation, both the cited patent and the present application have been formally assigned to Geron Corporation in their entirety, as can be evidenced from the respective filing papers.

Withdrawal of the rejections under § 103 is respectfully requested.

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[12] A greater than expected result is an evidentiary factor pertinent to the legal conclusion of the obviousness vel non of the claims at issue. That a claimed composition (e.g., of A and B) showed an additive result when a diminished result would have been expected is persuasive of nonobviousness even though the result may be equal to that of one component alone (e.g., B). *In re Corkill,* 226 USPQ 1005 (Fed. Cir. 1985).

[13] Evidence developed after the patent grant is not excluded from consideration, for understanding of the full range of an invention is not always achieved at the time of filing the patent application. *Knoll Pharmaceutical Co. v. Teva Pharmaceuticals USA, Inc.,* 70 USPQ2d 1957 (Fed. Cir. 2004). The PTO erred in ruling that an applicant's arguments and evidence concerning the advantages of the claimed invention's modification of the prior art should not be considered when the applicant's specification was "virtually silent" about the modification's advantages and failed to state that the modification solved any particular problem or achieved an unexpected result. *In re Chu.* 36 USPQ2d 1089 (Fed. Cir. 1995).

Double patenting

Claims 27-38 and 40 stand rejected for obviousness-type double patenting over certain claims of U.S. Patent 6,777,203 and U.S. Patent 6,610,839. Office Action states that the claims of the cited patent cover the hTERT promoter linked to a heterologous encoding region, and therefore cover the invention claimed in the present application.

Applicant respectfully disagrees. The proper test is not whether the previous patents read on the present invention, but whether the present invention is patentably distinct. In undertaking this analysis, the claims of the previous patents are compared with the claims at issue, absent of other subject matter that may be disclosed in the specifications[14]. Notwithstanding any overlap between the claims, the invention claimed here is patentably distinct over the claims in the earlier patents, because there is nothing in the *claims* of the earlier patents that refers to or suggests linking the hTERT promoter to *a gene that controls replication or assembly* of a viral vector.

Withdrawal of these rejections is respectfully requested.

Information Disclosure Statement

Applicant is grateful to the Examiner for considering the references provided in the previous Information Disclosure Statements. The few references not initialed on the PTO-1449 are believed to be cumulative to what has already been made of record in the application.

A copy of the Irving article and cover pages from the other four references referred to in footnotes 8-11 are provided herewith for the convenience of the Examiner. Full copies of the articles are available from public sources, and will be filed into this application as part of an Information Disclosure Statement so that they can formally be made of record in the application.

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[14] MPEP § 804 (II)(B)(1)(a) says the following: In resolving the issue of double patenting, [the question is] whether the invention defined in a claim in the application would have been an obvious variation of the invention defined in a claim in the patent. See, e.g., *In re Berg*, 46 USPQ2d 1226 (Fed. Cir. 1998). . . . Unless a claimed invention in the application would have been obvious over a claimed invention in the patent, no double patenting rejection of the obvious-type should be made.

PATENT
09/615,039
Docket 019/251c

Request for Interview

Applicant respectfully requests that all outstanding rejections be reconsidered and withdrawn. The application is believed to be in condition for allowance, and a prompt Notice of Allowance is requested.

In the event that the Examiner determines that there are other matters to be addressed, applicant hereby requests an interview by telephone.

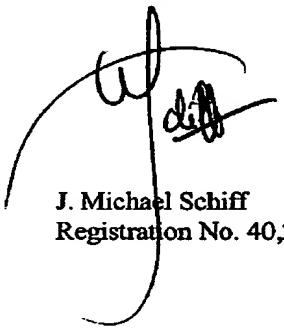
Fees Due

No fee is required with respect to the amendments to the claims, since there are only 20 claims and 3 independent claims currently pending in the application.

Enclosed with this Amendment is authorization to charge applicant's Deposit Account for the extension of time.

Should the Patent Office determine that a further extension of time or any other relief is required for further consideration of this application, applicant hereby petitions for such relief, and authorizes the Commissioner to charge the cost of such petitions and other fees due in connection with the filing of these papers to Deposit Account No. 07-1139, referencing the docket number indicated above.

Respectfully submitted,



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